116-043

UNITED STATES PATENT APPLICATION OF

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for

TREATMENT OF WARTS WITH TELLURIUM COMPOUNDS

BACKGROUND OF THE INVENTION:

Field of the Invention

This invention relates to the treatment of various warts.

Description of the Related Art

In U.S. 4,752,614,which is incorporated by reference, the use of certain tellurium compounds as anti-viral agents in plants or animals is disclosed. The virus that is exemplified is West Nile Virus. There is no known disclosure in the prior art of the use of tellurium compounds for the treatment of viral infections in humans.

Verrucae or warts as verrucae are commonly known, are generally defined as a contagious, epithelial tumor caused by at least 35 different types of human papilloma virus (HPV). Viral warts have been diagnosed in patients without regard to age or sex. The incidence of warts is most common in older children and is least common in persons of advanced age. Warts most often occur on the skin but may occur at any location in the body and my spread by auto-innoculation. In some cases complete regression occurs after several months with or without treatment with recurrence at the same or at different locations. The types of warts include common (verruca vulgaris, plantar, palmar and periungal); flat; genital (Condylomata acuminata); butcher's; malignant epidermodyspasia verruciformis; mepidermodysplasia verruciformis; cutnaeous warts in immunosuppressed patients; laryngeal papillomas; and oral papilloma. Each of these conditions has been liked to specific types or groups of papilloma viruses. Various topical and/or surgical techniques have been used for treating warts but no method

of treatment has been consistently effective. Surgical treatments have resulted in discomfort, prolonged healing and the formation of scars and/or keloids to a greater or lesser extent. Accordingly, a need exists for an improved method of treating warts.

SUMMARY OF THE INVENTION:

The subject invention pertains to a method for treatment of warts which comprises the administration of an effective amount of a tellurium compound to one who is afflicted with warts. The method of treatment includes the topical and systemic administration of a telliurium compound

Accordingly, it is a primary object of the invention to provide a method for the treatment of warts which comprises the topical application of an effective amount of a tellurium compound to a wart.

It is also an object of this invention to provide a method for the treatment of warts which comprises the systemic administration of an effective amount of a tellurium compound to an afflicted patient.

It is also an object of this invention to provide a method for the treatment of warts which avoids the scaring and prolonged healing that accompanies surgical removal of warts.

These and other objects of the invention will become apparent from a review of the specification.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a photograph prior to treatment of a patient afflicted with condyloma warts.

Fig. 2 is a photograph after about two weeks of treatment as described in Example 1.

Fig. 3 is a photograph after about four weeks of treatment as described in Example 1.

Fig. 4 is a photograph after about six weeks of treatment as described in Example 1.

Fig. 5 is a photograph after about eight weeks of treatment as described in Example 1.

Fig. 6 is a photograph of the treatment of a verucca wart as described in Example 2 at the beginning of treatment.

Fig. 7 is a photograph after about two weeks of treatment as described in Example 2.

Fig. 8 is a photograph after about four weeks of treatment as described in Example 2.

Fig. 9 is a photograph of the treatment of verucca warts as described in Example 3 at the beginning of treatment.

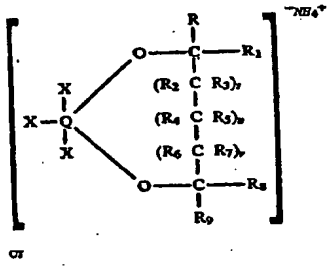
Fig. 10 is a photograph after about two weeks of treatment as described in Example 3.

Fig. 10 is a photograph after about two weeks of treatment as described in Example 3.

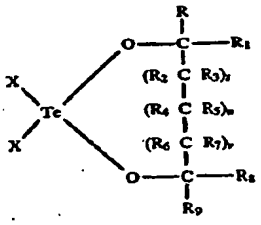
Fig. 11 is a photograph after about four weeks of treatment as described in Example 3.

DETAILED DESCRIPTION OF THE INVENTION:

The tellurium compounds for use in the invention include those of the formula:



or



or

TeO_2 or complexes of TeO_2

(C)

or

$PhTeCl_3$

(D)

or

TeX_4, when X is Cl, Br or F

or the following complex: $TeO_2.HOCH_2CH_2OH.NH_4Cl$;

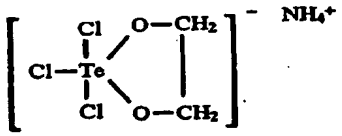
or

$(C_6H_5)_4P+(TeCl_3(O_2C_2H_4))-$ (E)

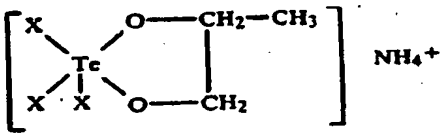
wherein t is 1 or 0; u is 1 or 0; v is 1 or 0; R, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are the same or different and are independently selected from the group consisting of hydrogen, hydroxyalkyl of 1 to 5 carbons, hydroxy, alkyl or from 1 to 5 carbon atoms, halogen, haloalkyl of 1 to 5 carbon atoms, carboxy, alkylcarbonylalkyl of 2 to 10 carbons, alkanoyloxy of 1 to 5 carbon atoms, carboxyalkyl of 1 to 5 carbons atoms, acyl, amido, cyano, amidoalkyl of 1 to 5 carbons, N-monoalkylamidoalkyl of 2 to 10 carbons, N,N-dialkylamidoalkyl of 4 to 10 carbons, cyanoalkyl of 1 to 5 carbons alkoxy of 1 to 5 carbon atoms, alkoxyalkyl of 2 to 10 carbon atoms and -COR_{10} wherein R_{10} is alkyl of 1 to 5 carbons; and X is halogen; while the ammonium salt is illustrated, it is understood that other pharmaceutically acceptable salts such as K+ are within the scope of the invention. The compounds with the five membered rings are preferred.

As used herein and in the appended claims, the term alkyl of 1 to 5 carbon atoms includes straight and branched chain alkyl groups such as methyl; ethyl; n-propyl; n-butyl, and the like; the term hydroxyalkyl of 1 to 5 carbon atoms includes hydroxymethyl; hydroxyethyl; hydroxy-n-butyl; the term halkoakyl of 1 to 5 carbon atoms includes chloromethyl; 2-iodoethyl; 4-bromo-n-butyl; iodoethyl; 4-bromo-n-pentyl and the like; the term alkanoyloxy of 1 to 5 carbon atoms

includes acetyl, propionyl, butanoyl and the like; the term carboxyalkyl includes carboxymethyl, carboxyethyl, ethylenecarboxy and the like; the term alkylcarbonylalkyl includes methanoylmethyl, ethanoylethyl and the like; the term amidoalkyl includes $-CH_2CONH_2$; $-CH_2CH_2CONH_2$; $-CH_2CH_2CH_2CONH_2$ and the like; the term cyanoalkyl includes $-CH_2CN$; $-CH_2CH_2CN$; $-CH_2CH_2CH_2CN$ and the like; the alkoxy, of 1 to 5 carbon atoms includes methoxy, ethoxy, n-propoxy, n-pentoxy and the like; the terms halo and halogen are used to signify chloro, bromo, iodo and fluoro; the term acyl includes $R_{16}CO$ wherein R_{16} is H or alkyl of 1 to 5 carbons such as methanoyl, ethanoyl and the like; the term aryl includes phenyl, alkylphenyl and naphthyl; the term N-monoalkylamidoalkyl includes $-CH_2CH_2CONHCH_3$, $-CH-_2CONHCH_2CH_3$; the term N,N-dialkylamidoalkyl includes $-CH_2CON(CH_3)_2$; $CH_2CH_2CON(CH_2-CH_3)_2$. The tellurium based compounds that are preferred include those of the formula:



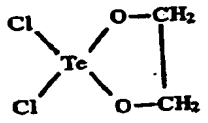
and



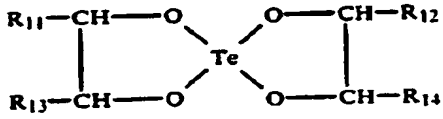
wherein X is halogen. The preferred halogen species is

chloro.

Other compounds which are based on tellurium and may be used in the practice of the invention include $PhTeCl_3$, TeO_2 and TeX_4 $(C_6H_5)_4$ P+ $(TeCl_3(O_2C_2H_4))$- (Z. Naturforsh, 36, 307-312 (1981). Compounds of the following structure are also included:



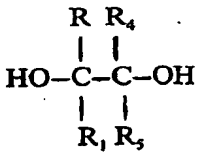
Other compounds useful for the practice of invention include:



wherein R_{11}, R_{12}, R_{13} and R_{14} are independently selected from the group consisting of hydrogen, hydroxy-alkyl of 1-5 carbons atoms, hydroxy and alkyl of 1-5 carbons atoms.

Useful dihydroxy compounds for use in the preparation of compounds of structure A or B, include those of formula I wherein R, R_1, R_4 and R_5 are as shown in the Table:

TABLE



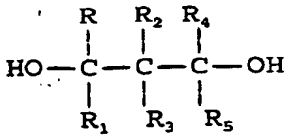
(I)

R	R_1	R_4	R_5
H	H	H	H

H	Cl	H	H
H	OCH_3	H	H
H	$COOCH_3$	H	H
H	H	CN	H
H	CHO	H	H
H	H	COOH	H
H	CH_2COOH	H	H
H	H	CH_2COOCH_3	H
H	I	H	H
H	H	Br	H
H	H	$CONH_2$	H
H	H	CH_2OH	H
H	COOH	H	H

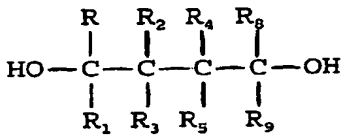
Other dihydroxy compounds for use in the preparation of compounds A and B include those of formula II wherein R, R_1, R_2, R_3, R_4 and R_5 are as shown in the Table:

(II)



R	R_1	R_2	R_3	R_4	R_5
H	H	H	H	H	H
H	H	Cl	H	H	H
H	CH_2OH	H	H	H	H
H	H	OH	H	H	H
H	H	H	CH_3	H	H
H	H	H	CH_2Cl	H	H
H	H	H	COOH	H	H
H	H	H	CH_2COOH	H	H
H	H	H	CHO	H	H
H	H	H	H	H	CH_2CHO
H	H	$CONH_2$	H	H_2	CH_3
H	H	H	CN	H	H
H	H	H	H	CH_2COHN_2	H
H	H	H	$COOCH_3$	H_3	H
H	H_3	OCH_3	H	H	H

Other dihydroxy compounds for use in making compound of formula A and B include those of formula III wherein R, R_1, R_2, R_3, R_4 and R_5 are as shown in the Table.

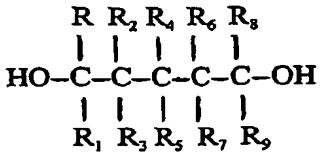


(III)

R	R_1	R_2	R_3	R_4	R_5	R_8	R_9
H	H	H	H	H	H	H	H
H	H	Cl	H	H	H	H	H
H	H	H	H	Br	H	H	H
H	H	OCH_3	H	H	H	H	H
H	H	$CONH_2$	H	H	H	H	H
H	Br	H	H	H	H	H	H
H	H	H	H	CH_2COOH	H	H	H
H	H	Cl	Cl	H	H	H	H
H	CH_2COOH	H	H	H	H	H	H
H	H	CH_3	H	H	H	H	H
H	CH_3	H	H	H	H	H	H
H	CH_2Cl	H	H	H	H	H	H
H	H	H	I	H	H	H	H
H	CH_2CN	H	H	H	H	H	H
H	H	H	H	CH_2CH_2OH	H	H	H

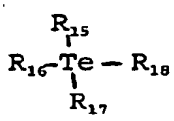
Additional dihydroxy compounds include those of formula IV wherein R, R_1, R_2, R_3, R_4 and R_5 are as shown in the Table.

(IV)



R	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9
H	H	H	H	H	H	H	H	H	H
H	H	Cl	H	H	H	Cl	H	H	H
H	H	Cl	Cl	H	H	H	H	H	H
H	H	$CONCH_3$	H	H	H	Br	H	H	H
H	H	Br	H	H	H	$CON(CH_3)_2$	H	H	H
H	H	H	OCH_3	H	H	H	H	H	H
H	H	H	H	OCH_3	H	H	H	H	H
H	H	H	H	CH_2COOH	H	H	H	H	H
H	H	COOH	H	H	H	H	H	H	H
H	CH_3	H	H	H	H	H	H	H	H
CH_3	H	H	H	H	CH_3	H	H	H	H
H	CH_2CH_3	H	H	H	H	H	Cl	H	H
H	CH_2CN	H	H	CH_2OH	H	H	H	H	H
H	H	H	I	H	H	H	H	CN	H
H	CH_2CH_2COOH	H	H	H	H	H	H	H	H
H	H	CHO	H	H	H	H	H	H	H
H	H	H	F	H	H	H	H	H	H

Compounds of the following formula are also included:



herein R_{15}, R_{16}, R_{17} and R_{18} are independently selected from halogen, alkyl of 1-5 carbons; aryl, acyl of 1-5 carbon hydroxyalkyl of 1-5 carbons and aminoalkyl of 1-5 carbons may be made by reacting the appropriate di, tri or tetrahalotelluride with the appropriate hydroxy compound which may be of the formula: $HO-R_{19}$; wherein R_{19}; is alkyl of 1 to 5 carbons, haloalkyl of 1 to 5 carbons, aryl, alkylaryl, alkylamido of 1 to 5 carbons, alkylcarbonyl of 1 to 5 carbons, cyanoalkyl of 1 to 5 carbons, cyanoalkyl of 1 to 5 carbons, and an alkoxyalkyl of 2 to 10 carbons. Specific examples of R_{16} include methyl, ethyl, n-propyl, phenyl, tolyl, amidoethyl, cyanomethyl, methyloxymethyl and CH_2CH_2COOH.

These compounds are described in United States Patent No. 4,761,490 which is incorporated by reference. In addition, $TeCl_4$; $TeBr_4$ and compounds which give in aqueous solution TeO_2 preferably in the form of a complex such as for example TeO_2 complex with citric acid or ethylene glycol.

The preferred compound is ammonium trichloro (dioxoethylene-O,O') tellurate.

The topical treatment of warts involves contacting the affected area with a liquid or semisolid composition of the tellurium compound in a liquid or semisolid vehicle. The liquid vehicle may comprise water, dimethyl sulfoxide, propylene glycol, ethanol and solvents containing polyhydroxy groups.

The semisolid vehicle may comprise a hydrophilic or a

hydrophobic ointment base such as petrolatum U.S.P., or water washable cream type base such as polyethylene glycol ointment U.S.P.

The concentration of the tellurium compound in the topical composition may vary from 1 to 40wt% and more preferably from 15 to 25wt.% In selected cases where warts are found on cornified epitheilial tissue, it may be desirable to coadminister a keratolytic agent such as salicylic acid at concentrations of 20 to 50wt% of the total weight of the tellurium containing composition.

Systemic treatment may be achieved by oral or parenteral administration of the tellurium compound at a dose of 0.1 to 5.0 mg/kg of body weight, preferably 1 to 3mg/kg given daily in divided doses.

The preferred method of administration will be determined by the type of wart that is being treated and the location of the wart. The optimum dose and frequency may be determined by the individualized response to the clinical treatment of particular cases.

EXAMPLE 1

A human patient with *condyloma acuminatum* in the perianal region is treated with a dispersion of ammonium trichloro (dioxoethylene-O,O') tellurate that is prepared by dissolving a sufficient amount of the tellurate compound in dimethyl sulfoxide to make a 40%w/w solution and then combining that solution with an equal weight of petrolatum, U.S.P.to make a 20%w/w dispersion of the tellurate. This formulation is topically applied twice daily to cover the affected area for a period of about 4 weeks. After a few days the lesion

changes color from pink to grey-black and after about 4 to 5 weeks, the lesion sloughs off without leaving any scarring. Figs. 1-5 show the effect of the therapy on the condyloma at bi-weekly intervals during the period of treatment

EXAMPLE 2

A human patient with a verrucca lesion on the hand is treated with the same dispersion of ammonium trichloro (dioxoethylene-O,O') tellurate that was prepared in Example 1. The formulation was applied twice daily for a period of about 4 weeks. After about four weeks the wart sloughs off and leaves no scar on the treated area. Figs. 6-8 show the progress of treatment at biweekly intervals.

EXAMPLE 3

A human patient with multiple verrucca lesions on the hand is treated with the same dispersion of ammonium trichloro (dioxoethylene-O,O') tellurate that was prepared in Example 1. The formulation was applied twice daily for a period of about 4 weeks. After about four weeks the wart sloughs off and leaves no scar on the treated area. Figs. 9-11 show the progress of treatment at biweekly intervals.